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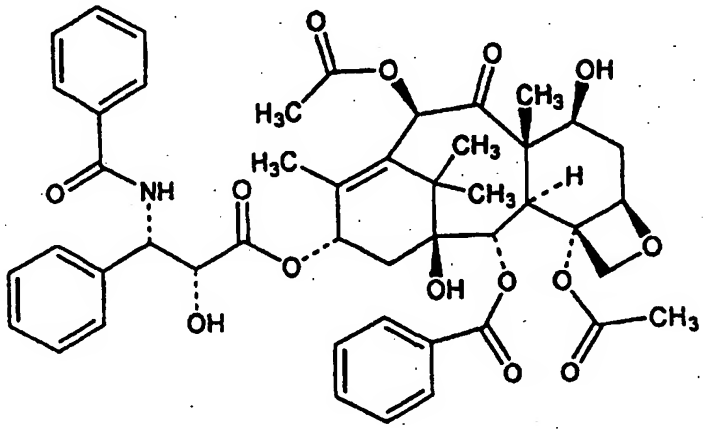
(54) Title: STENT HAVING DRUG CRYSTALS THEREON



(57) Abstract

A medical device for insertion into a mammalian body, wherein the medical device has a crystalline therapeutic agent thereon. Also provided is a method of delivering a therapeutic agent to a target location within a mammalian body. The method comprises the steps of placing crystals of the therapeutic agent on a medical device, and delivering the medical device to the target location.

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STENT HAVING DRUG CRYSTALS THEREON

Field of the Invention

The present invention relates to the localized delivery of therapeutic agents, and more particularly to the localized delivery of crystalline therapeutic agents to target locations within a body.

Background of the Invention

The systemic administration of drug agents, such as by transoral or intravenous means, treats the body as a whole even though the disease to be treated may be localized. In such a case, systemic administration may not be desirable because the drug agents often have unwanted effects on parts of the body that are not intended to be treated, or because treatment of the diseased part of the body requires a high concentration of drug agent that may not be achievable by systemic administration.

It is therefore often desirable to administer drug agents at localized sites within the body. Common examples include cases of localized disease such as heart disease, or occluded body lumens. Various methods have been proposed for such localized drug administration. For example, U.S. Patent No. 5,304,121, which is incorporated herein by reference, discloses a method of delivering water-soluble drugs to tissue at desired locations of a body lumen wall. The method generally includes the steps of impregnating a hydrogel polymer on a balloon catheter with an aqueous drug solution, inserting the catheter into a blood vessel to a desired

location, and expanding the catheter balloon against the surrounding tissue to allow the release of the drug.

One potential drawback to conventional localized drug administration is the uncontrolled rapidity at which the drug or drug solution is released from the delivery device. It is often desired, if not necessary, to control and/or lengthen the time period over which the drug is released. For example, it might be advantageous to lengthen the release time from seconds to minutes, or from minutes to hours, days, or even weeks. Exceptionally long release times as long as several months are often desired, for example, where the drug is released from an implanted device such as a stent. Moreover, it is often desired to control the release rate of the drug over prolonged periods of time.

Summary of the Invention

In one aspect, the present invention provides a medical device for insertion into a mammalian body, wherein the medical device has a therapeutic agent applied to at least a portion of a surface thereof, and the therapeutic agent is in a crystalline form.

In another aspect, the present invention provides a method of delivering a therapeutic agent to a target location within a mammalian body. The method comprises the steps of placing crystals of the therapeutic agent on at least a portion of a surface of a medical device, and delivering the medical device to the target location.

One advantage of the present invention is that it retards the release of therapeutic agents from a localized drug delivery system.

Another advantage of the present invention is that it provides for a controlled release rate of therapeutic agents from a localized drug delivery system.

Definitions

As used herein, the following terms are defined as follows:

"Balloon catheter" refers to a tubular instrument with a balloon or multiple balloons that can be inflated or deflated without removal after insertion into the body.

"Biodegradable" refers to a substance that can be substantially chemically degraded or decomposed by exposure to bodily tissue or fluids.

"Biostable" refers to a substance that is not substantially chemically degraded or decomposed by exposure to bodily tissue or fluids.

"Crystal" refers to a solid of regular shape and, for a given material, characteristic angles, wherein the individual atoms or molecules within the crystal take up regular positions with respect to one another.

"Crystallization" refers to the process whereby a material assumes a crystalline form when a vapor or liquid becomes solidified, or a solute precipitates from solution under proper conditions.

"Drug" and "therapeutic agent" are used interchangeably to refer to any substance used in the prevention, diagnosis, alleviation, treatment or cure of disease.

"Stenosis" refers to a stricture of any bodily canal.

"Stent" refers to any tubular structure used to maintain or support a bodily orifice or cavity.

Brief Description of the Drawings

Fig. 1 is a scanning electron microphotograph of medical device having crystals of therapeutic agent thereon.

Fig. 2 is a scanning electron microphotograph of medical device having a layer of therapeutic agent crystals thereon.

Fig. 3 is a graph showing the release profiles of paclitaxel from coated stents, for paclitaxel in both crystalline and non-crystalline form.

Detailed Description

The present invention makes use of crystals of therapeutic agents to retard the release of the therapeutic agent when delivered to a target location within a mammalian body. Moreover, the release of the therapeutic agent in its crystalline form is controlled in that the therapeutic agent is released at a characteristic rate or release profile over time.

In one aspect, the present invention provides a medical device for insertion into a mammalian body, wherein the medical device has a therapeutic agent applied to at least a portion of a surface thereof, and the therapeutic agent is in the form of crystals.

The therapeutic agent used in the present invention includes, for example, any pharmaceutically active material that can be crystallized. Such therapeutic agents may include biologically active solutes such as anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, PPACK (dextrophenylalanine proline arginine chloromethylketone), rapamycin, probucol, and verapimil; angiogenic and anti-angiogenic agents; anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid; anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, and mesalamine; antineoplastic/ antiproliferative/ anti-mitotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin and thymidine kinase inhibitors; anesthetic agents such as lidocaine, bupivacaine, and ropivacaine; anti-coagulants such as D-Phe-Pro-Arg chloromethyl keton, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin anticodies, anti-platelet receptor antibodies, aspirin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet factors; vascular cell growth promotors such as growth factors, growth factor receptor antagonists, transcriptional activators, and translational promotors;

vascular cell growth inhibitors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; cholesterol-lowering agents; vasodilating agents; agents which interfere with endogeneus vascoactive mechanisms, and combinations thereof. Preferred therapeutic agents for use in the present invention are paclitaxel and derivatives thereof.

For the localized delivery of therapeutic agent to a target location within a mammalian body, the therapeutic agent is placed on a medical device for insertion into the body to a target location. The medical device used in the present invention is any insertable or implantable device including, for example, stents, balloon catheters, blood clot filters, vascular grafts, stent grafts, aneurysm filling coils, intralumenal paving systems, etc., as are known in the art. A preferred medical device for use with the present invention is an implantable device such as a stent, for which the present invention allows for the continued release of therapeutic agents therefrom for extended time periods of up to several months.

As shown in Fig. 1, the therapeutic agent is applied to the medical device, for example, such that isolated, individual crystals 101 exist on the surface of the medical device 102. Alternatively, the therapeutic agent is applied to the medical device such that a layer 201 of crystals exists on at least a portion of the medical device 202. In either case, the crystals of the therapeutic agent are optionally placed within or over a polymer coating, which at least partially coats the medical device as described further herein.

The crystals of the therapeutic agent are applied to the medical device by any suitable method. In one embodiment, the crystals are formed by the following steps: i) placing a therapeutic agent, while in a

non-crystalline form, into solution with a polymer in which the therapeutic agent is substantially soluble; ii) applying the solution onto at least a portion of a medical device as a coating; iii) drying the coating to form a dry coating wherein the therapeutic agent is dispersed in the polymer; iv) exposing the coated medical device to a non-solvent (*i.e.*, a material in which the therapeutic agent is relatively insoluble); and v) allowing the therapeutic agent to diffuse out of the coating to the interface between the coating and the non-solvent, whereupon the therapeutic agent crystallizes on the surface of the coating. Alternatively, where the non-solvent can diffuse into the coating or where the coating is otherwise porous, the non-solvent penetrates the coating such that the therapeutic agent crystallizes within the coating.

When used in the present invention, the polymer coating comprises any polymeric material in which the therapeutic agent is substantially soluble. The polymer is, for example, hydrophilic, hydrophobic, and/or biodegradable. For example, the polymer is selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyurethanes, silicones, polyorthoesters, polyanhydrides, polycarbonates, polypropylenes, polylactic acids, polyglycolic acids, polycaprolactones, polyhydroxybutyrate valerates, polyacrylamides, polyethers, and mixtures and copolymers thereof. Coatings from polymer dispersions such as polyurethane dispersions (BAYHYDROL, etc.) and acrylic latex dispersions are also within the scope of the present invention. A preferred polymer for use in the polymer coating of the present invention is polyurethane.

In another embodiment, the crystals are formed by the following steps: i) forming a miscible solution comprising the therapeutic agent, a solvent and a non-solvent, wherein the therapeutic agent is substantially soluble in the solvent and substantially insoluble in the non-

solvent, and wherein the solvent is miscible in, and more volatile than, the non-solvent; ii) applying the solution onto a medical device as a coating; and iii) allowing at least a portion of the solvent to evaporate from the coating, whereupon the therapeutic agent forms into crystals on the surface of the medical device.

In any embodiment of the invention, the therapeutic agent is applied to the medical device, while in solution or otherwise, by any suitable method. Preferred methods include spraying the device with the therapeutic agent or solution, and dipping the device into the therapeutic agent or solution. As an example, the thickness of the therapeutic agent, together with any polymer, is in the range of from 1 to about 50 microns. The thickness of such a coating is not, however, a critical feature of the present invention so long as a sufficient amount of therapeutic agent to provide a sustained or controlled release over a suitable or desired time period is provided.

The medical device is optionally at least partially coated with a polymer precoat for enhanced adhesion of the therapeutic agent. The polymer precoat should have a low solubility for the therapeutic agent. Preferred precoat materials include polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyurethanes, silicones, polyorthoesters, polyanhydrides, polycarbonates, polypropylenes, polylactic acids, polyglycolic acids, polycaprolactones, polyhydroxybutyrate valerates, polyacrylamides, polyethers, and mixtures and copolymers thereof.

The crystals of the therapeutic agent are optionally coated with a polymer topcoat for physical protection of the crystals, and/or as a barrier to premature release of the therapeutic agent, and/or to further retard or control the release rate of the therapeutic agent. The topcoat may be either biodegradable or biostable. If the topcoat is biodegradable, the therapeutic

agent is substantially released after the decomposition of the topcoat. If the topcoat is biostable, the therapeutic agent is substantially released by diffusion through the topcoat. Preferred biodegradable materials for the topcoat include polymers such as poly(L-lactic acid), poly(DL-lactic acid), polycaprolactone, poly(hydroxy butyrate), polyglycolide, poly(dioxanone), poly(hydroxy valerate), polyorthoester; copolymers such as poly (lactide-co-glycolide), polyhydroxy(butyrate-co-valerate), polyglycolide-co-trimethylene carbonate; polyanhydrides; polyphosphoester; polyphosphoester-urethane; polyamino acids; polycyanoacrylates; biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid; and mixtures thereof. Preferred biostable materials for the topcoat include polymers such as polyurethane, silicones, polyesters, polyolefins, polyamides, polycaprolactam, polyimide, polyvinyl chloride, polyvinyl methyl ether, polyvinyl alcohol, acrylic polymers and copolymers, polyacrylonitrile, polystyrene copolymers of vinyl monomers with olefins (such as styrene acrylonitrile copolymers, ethylene methyl methacrylate copolymers, ethylene vinyl acetate), polyethers, rayons, cellulosics (such as cellulose acetate, cellulose nitrate, cellulose propionate, etc.), parylene and derivatives thereof; and mixtures and copolymers thereof.

When used, the precoat and topcoat materials are applied by any suitable method such as, for example, spraying, dipping, and vapor deposition such as plasma deposition, physical vapor deposition, chemical vapor deposition, ion bombardment, ion-beam sputter deposition, ion-beam assisted deposition, and sputtering.

The present invention is further described with reference to the following non-limiting examples.

Example 1 - Formation of Paclitaxel Crystals from Coated Stents by Exposure to a Non-solvent

Paclitaxel (TAXOL®) was placed into solution by mixing about

0.19 milligrams of polyurethane, about 0.10 milligrams reagent paclitaxel, and about 27.15 milligrams of 99.9% ACS HPLC-grade chloroform stabilized with ethanol. The mixture was mixed with a magnetic stirrer for about one hour to form a solution consisting of about 1.0% solids and having a polyurethane-to-paclitaxel ratio of about 65-to-35.

The paclitaxel solution was sprayed onto 9 millimeter NIR® (Medinol, Tel Aviv, Israel) stents with a Badger Air Brush model 350 sprayer at a pressure of about 19 psi for about 1 minute. The distance between the stents and the spray nozzle was about 2.5 inches. A uniform coating of approximately 13 microns was obtained. The coating was dried for about 30 minutes at about 65°C to remove solvent, followed by thorough drying for about 3 hours at 70°C under vacuum.

Paclitaxel crystals were formed on some of the stents by exposure to about 5 milliliters of distilled water for about 1.5 days while stirring at room temperature. The stents were thereafter removed from water and air dried. Scanning electron microscopy was used to confirm the presence of paclitaxel crystals on the surface of the coated stents. The crystals were up to approximately 200 microns in length.

Example 2 - Release of Paclitaxel from Coated Stents

Stents coated with paclitaxel in both crystalline and non-crystalline form were made in accordance with Example 1. The in-vitro release of paclitaxel from these stents was measured as a function of time. As shown in Fig. 3, the paclitaxel in crystalline form was released at a slower rate than the paclitaxel dispersed in the polyurethane coating on the coated stents.

Example 3 - Application of Topcoat onto Coated Stents

Topcoats are applied to the coated stents described in Example 1.

The topcoats comprise either poly(lactide-co-caprolactone) in solution with 99.9% ACS HPLC-grade chloroform stabilized with ethanol, or polyvinyl alcohol in solution with deionized water.

Topcoat solutions are applied to coated stents by spraying with a Badger Air Brush model 350 sprayer at a pressure of about 19 psi for about 10 seconds. The distance between the stents and the spray nozzle is about 2.5 inches. A uniform coating of approximately 1 to 2 microns is obtained.

Example 4 - Formation of Paclitaxel Crystals by Spraying Stents with a Solvent / Non-solvent

Paclitaxel is placed in solution with acetonitrile, a solvent. Water, a non-solvent, is added in an amount that does not result in precipitation of the paclitaxel from the acetonitrile / water mixture. The mixture of paclitaxel, acetonitrile and water is sprayed onto a NIR® (Medinol, Tel Aviv, Israel) stent with a Badger Air Brush model 350 sprayer at a pressure of about 19 psi for about 1 minute. The distance between the stents and the spray nozzle is about 2.5 inches. A uniform coating of approximately 13 microns is obtained. As the acetonitrile evaporates from the coating, paclitaxel crystals form.

The present invention provides for the controlled, localized delivery of therapeutic agents to target locations within a mammalian body. The invention makes use of crystals of such therapeutic agents to retard and/or control the rate of release. Those with skill in the art may recognize various modifications to the embodiments of the invention described and illustrated herein. Such modifications are meant to be covered by the spirit and scope of the appended claims.

We claim:

1. A medical device for insertion into a mammalian body, wherein:
said medical device has a therapeutic agent applied to at least a portion of a surface thereof; and
said therapeutic agent is in the form of crystals.

2. The medical device of claim 1, wherein said medical device is a stent.

3. The medical device of claim 1, wherein said medical device is a balloon catheter.

4. The medical device of claim 1, wherein said therapeutic agent comprises paclitaxel.

5. The medical device of claim 1, further comprising a polymer coating on said medical device.

6. The medical device of claim 5, wherein said polymer coating is biodegradable.

7. The medical device of claim 5, wherein said polymer coating is biostable.

8. The medical device of claim 5, wherein said polymer coating comprises polyurethane.

9. The medical device of claim 5, wherein said crystals are dispersed within said polymer coating.

10. The medical device of claim 5, wherein said crystals are positioned

on at least a portion of the outer surface of said polymer coating.

11. A method of delivering a therapeutic agent to a target location within a mammalian body, said method comprising the steps of:

placing crystals of said therapeutic agent on at least a portion of a surface of a medical device; and

delivering said medical device to said target location.

12. The method of claim 11, wherein said step of placing crystals of said therapeutic agent on a medical device comprises the steps of:

mixing said therapeutic agent, while in a non-crystalline form, with a polymer to form a therapeutic agent / polymer mixture;

applying said therapeutic agent / polymer mixture onto at least a portion of a surface of said medical device as a coating;

exposing said coated medical device to a non-solvent to form an interface between said coating and said non-solvent, said therapeutic agent being substantially insoluble in said non-solvent.

13. The method of claim 12, wherein said therapeutic agent is soluble in said polymer.

14. The method of claim 12, further comprising the step of coating said crystals with a polymer topcoat layer.

15. The method of claim 14, wherein said polymer topcoat layer is biodegradable.

16. The method of claim 14, wherein said polymer topcoat layer is biostable.

17. The method of claim 12, wherein said step of applying said therapeutic agent / polymer mixture onto said medical device as a coating comprises the step of spraying said mixture onto said medical device.

18. The method of claim 12, wherein said step of applying said therapeutic agent / polymer mixture onto said medical device as a coating comprises the step of dipping said medical device into said mixture.

19. The method of claim 11, wherein said step of placing crystals of said therapeutic agent on a medical device comprises the steps of:

forming a miscible solution comprising said therapeutic agent, a solvent, and a non-solvent, wherein said therapeutic agent is substantially soluble in said solvent and substantially insoluble in said non-solvent, and wherein said solvent is more volatile than said non-solvent;

applying said solution onto at least a portion of a surface of said medical device as a coating; and

allowing at least a portion of said solvent to evaporate, thus forming said crystals.

20. The method of claim 19, further comprising the step of coating at least a portion of said medical device with a polymer precoat layer before said step of applying said solution onto said medical device as a coating.

21. The method of claim 19, further comprising the step of coating said crystals with a polymer topcoat layer.

22. The method of claim 21, wherein said polymer topcoat layer is biodegradable.

23. The method of claim 21, wherein said polymer topcoat layer is biostable.

24. The method of claim 19, wherein said step of applying said solution onto at least a portion of a surface of said medical device as a coating comprises the step of spraying said solution onto said medical device.

25. The method of claim 19, wherein said step of applying said solution onto at least a portion of a surface of said medical device as a coating comprises the step of dipping said medical device into said solution.

26. A medical device having crystals thereon, said crystals comprising paclitaxel.

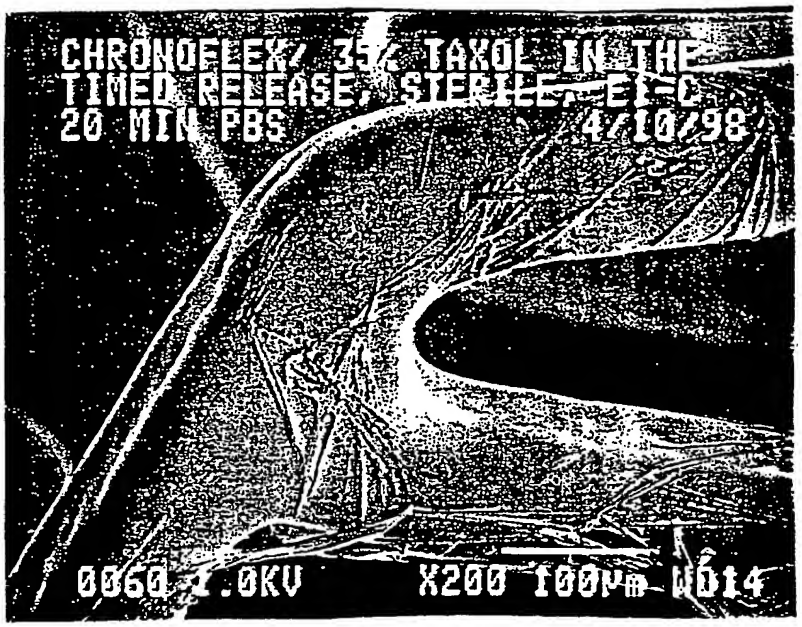

Fig. 1

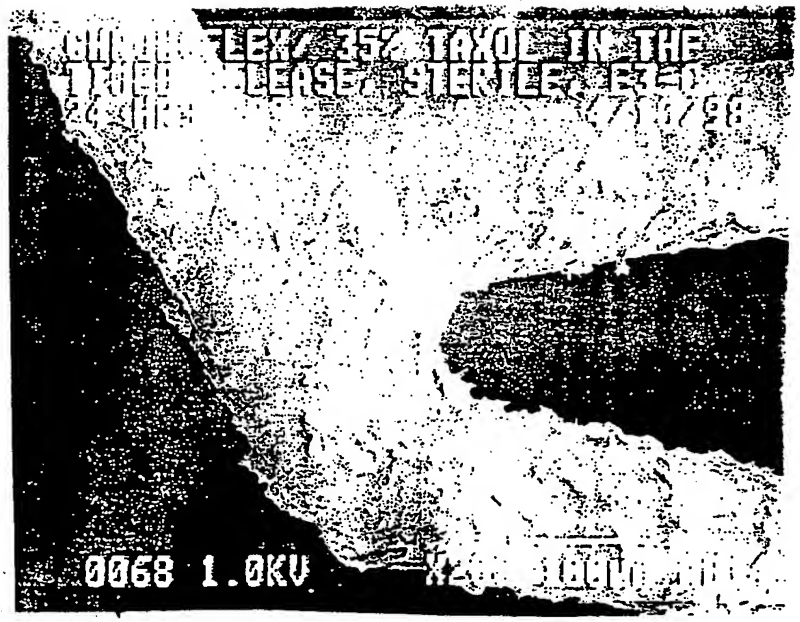

Fig. 2

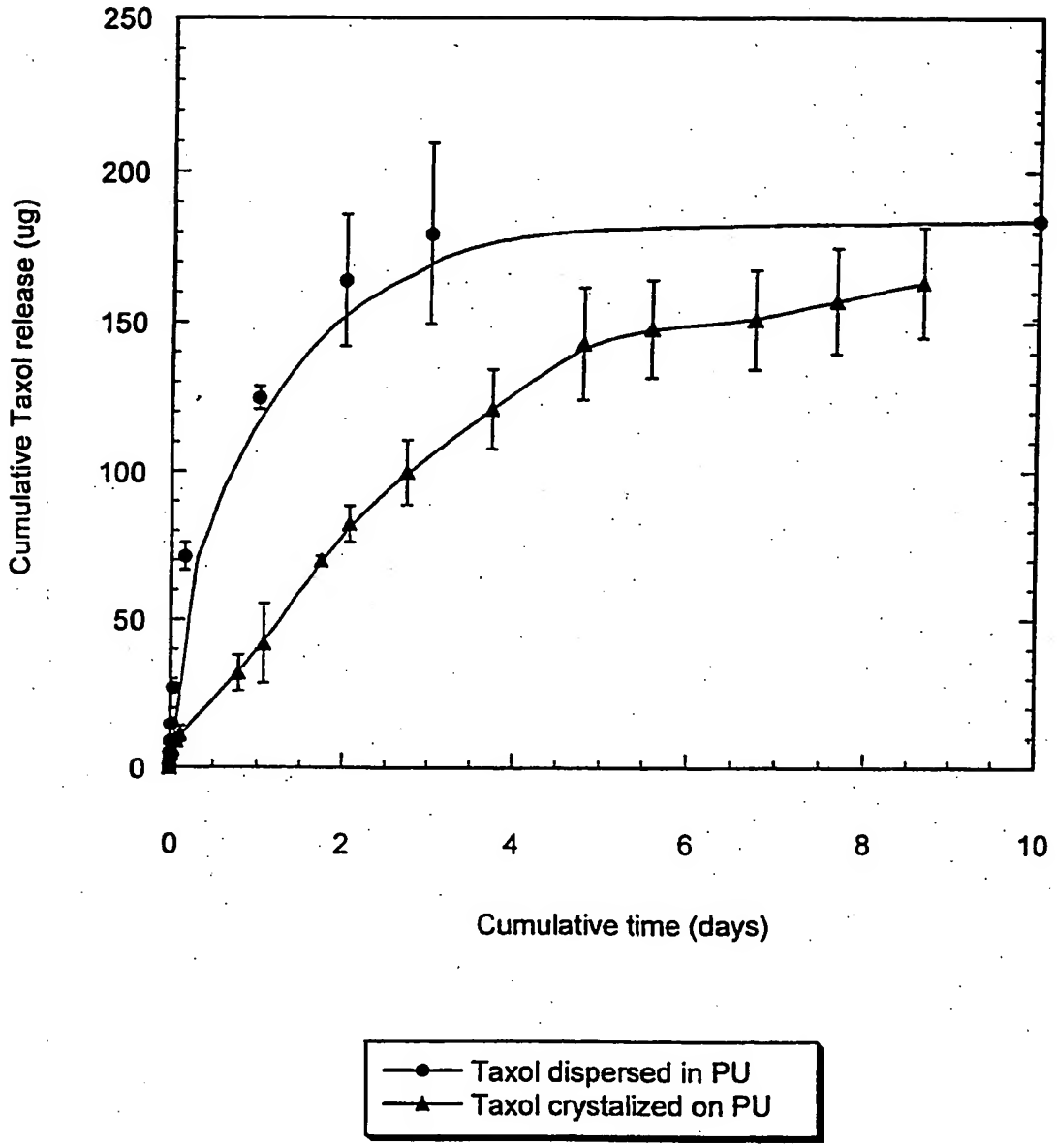
250
200
150
100
50
0
Cumulative Taxol release (ug)
0
2
4
6
8
10
Cumulative time (days)
Taxol dispersed in PU
Taxol crystalized on PU

Fig. 3

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 99/27279

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61L31/10 A61L29/10

According to International Patent Classification (IPC) or to both national classification and IPC

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 03036 A (ANGIOGENESIS TECH INC ;ARSENAULT A LARRY (CA); BURT HELEN M (CA);) 2 February 1995 (1995-02-02) example 9	1-26
X	WO 96 25176 A (RENO JOHN M ;KUNZ LAWRENCE L (US); NEORX CORP (US)) 22 August 1996 (1996-08-22) claims 4,8,11,18,27,32,36,45,49,53,57,61	1-26

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SCHIERHOLZ J M ET AL: "Investigation of a rifampin, fusidic-acid and mupirocin releasing silicone catheter" BIOMATERIALS,GB,ELSEVIER SCIENCE PUBLISHERS BV., BARKING, vol. 19, no. 22, November 1998 (1998-11), pages 2065-2074, XP004161481 ISSN: 0142-9612 abstract figure 5A page 2071, paragraph 4.2 -page 2072	1-3,5-25
X	WO 98 43618 A (NEORX CORP) 8 October 1998 (1998-10-08) example 18	1-26
X	KORNOWSKI RAN ET AL: "Slow-release taxol coated GRII stents reduce neointima formation in a porcine coronary in-stent restenosis model." 70TH SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION;ORLANDO, FLORIDA, USA; NOVEMBER 9-12, 1997, vol. 96, no. 8 SUPPL., 1997, page I341 XP000891206 Circulation 10/21/97, 1997 ISSN: 0009-7322 abstract	1-26
X	HAEHNEL I ET AL: "Local growth inhibitory effect of paclitaxel release by a biodegradable stent coating on vascular smooth muscle cells." 47TH ANNUAL SCIENTIFIC SESSION OF THE AMERICAN COLLEGE OF CARDIOLOGY;ATLANTA, GEORGIA, USA; MARCH 29-APRIL 1, 1998, vol. 31, no. 2 SUPPL. A, February 1998 (1998-02), page 278A XP000877498 Journal of the American College of Cardiology Feb., 1998 ISSN: 0735-1097 abstract	1-26
X	FARB ANDREW ET AL: "Paclitaxel polymer-coated stents reduce neointima." 70TH SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION;ORLANDO, FLORIDA, USA; NOVEMBER 9-12, 1997, vol. 96, no. 8 SUPPL., 1997, page I608 XP000891207 Circulation 10/21/97, 1997 ISSN: 0009-7322 abstract	1-26

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INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 99/27279

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	HAEHNEL I ET AL: "Local growth inhibitory effect of paclitaxel released by a biodegradable stent coating on vascular smooth muscle cells." XIXTH CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY TOGETHER WITH THE 32ND ANNUAL GENERAL MEETING OF THE ASSOCIATION OF EUROPEAN PAEDIATRIC CARDIOLOGISTS;STOCKHOLM, SWEDEN; AUGUST 24-28, 1997, vol. 18, no. ABSTR. SUPPL., 1997, page 460 XP000877497 European Heart Journal 1997 ISSN: 0195-668X abstract	1-26
X	MANIFOLD D K ET AL: "Taxol coated stents in oesophageal adenocarcinoma." DIGESTIVE DISEASE WEEK AND THE 99TH ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION;NEW ORLEANS, LOUISIANA, USA; MAY 16-22, 1998, vol. 114, no. 4 PART 2, 15 April 1998 (1998-04-15), page A27 XP000891205 Gastroenterology April 15, 1998 ISSN: 0016-5085 abstract	1-26
X	VOISARD R ET AL: "Paclitaxel-coated biodegradable stents inhibit proliferative activity and severely damage cytoskeletal components of smooth muscle cells from human coronary plaque material in vitro." XXTH CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY;VIENNA, AUSTRIA; AUGUST 22-26, 1998, vol. 19, no. ABST. SUPPL., August 1998 (1998-08), page 376 XP000891208 European Heart Journal Aug., 1998 ISSN: 0195-668X abstract	1-26

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1

INTERNATIONAL SEARCH REPORT

Intern. ıal Application No
PCT/US 99/27279

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	HAEHNEL IRIS ET AL: "Differential effect of a local paclitaxel release from a biodegradable stent coating on vascular smooth muscle cells and endothelial cells in a coculture model." 48TH ANNUAL SCIENTIFIC SESSION OF THE AMERICAN COLLEGE OF CARDIOLOGY;NEW ORLEANS, LOUISIANA, USA; MARCH 7-10, 1999, vol. 33, no. 2 SUPPL. A, February 1999 (1999-02), page 222A XP000877499 Journal of the American College of Cardiology Feb., 1999 ISSN: 0735-1097 abstract	1-26

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/27279

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-25
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 11-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-26 in part
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 27279

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-26 in part

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to those parts relating to stents coated with paclitaxel cristals.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr. ial Application No
PCT/US 99/27279

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9503036 A	02-02-1995	AT 154757 T	15-07-1997
		AU 6991198 A	16-07-1998
		AU 693797 B	09-07-1998
		AU 7119294 A	20-02-1995
		CA 2167268 A	02-02-1995
		CN 1130866 A	11-09-1996
		DE 69403966 D	31-07-1997
		DE 69403966 T	05-02-1998
		DK 706376 T	13-10-1997
		EP 0706376 A	17-04-1996
		EP 0797988 A	01-10-1997
		ES 2106553 T	01-11-1997
		GR 3024833 T	30-01-1998
		JP 9503488 T	08-04-1997
		NO 960226 A	18-03-1996
		NZ 268326 A	19-12-1997
		US 5886026 A	23-03-1999
		US 5716981 A	10-02-1998
		US 5994341 A	30-11-1999
WO 9625176 A	22-08-1996	AU 4985196 A	04-09-1996
		CA 2212537 A	22-08-1996
		EP 0809515 A	03-12-1997
		JP 11500635 T	19-01-1999
		US 5981568 A	09-11-1999
WO 9843618 A	08-10-1998	US 5981568 A	09-11-1999
		EP 0975340 A	02-02-2000